Fourier Transform Infrared Spectroscopy for the Analysis of Neutralizer-Carbomer and Surfactant-Carbomer Interactions in Aqueous, Hydroalcoholic, and Anhydrous Gel Formulations

Mohammad T. Islam,[1] Naír Rodríguez-Hornedo,[1] Susan Ciotti,[2] and Chrisita Ackermann[2]

[1]Department of Pharmaceutical Sciences, College of Pharmacy, University of Michigan, Ann Arbor, MI 48109
[2]Pfizer, Inc, 2800 Plymouth Rd, Ann Arbor, MI 48105

ABSTRACT

The objective of the present study is to evaluate the polymer-surfactant and polymer-neutralizer interactions in topical aqueous, anhydrous, and hydroalcoholic gel formulations using Fourier transform infrared (FTIR) spectroscopy. The gels were prepared by dispersing Carbomer (Carbopol 980) in water and ethanol for aqueous and anhydrous systems, respectively. Glycerol and propylene glycol were also added to ensure that the compositions of gels closely resembled those used in typical topical gel formulations. Comparisons of the spectra of Carbopol dispersions in aqueous, anhydrous, and hydroalcoholic systems, performed for the first time, show Carbopol-neutralizer and Carbopol-surfactant interactions vary depending on the nature of the solvents used for gel formation. Analysis of the spectra of aqueous gel formulations indicates significant presence of ionized carboxyl groups only at higher pH (~8.0). Drying of the aqueous gels causes a shift in the carbonyl stretch band toward higher energy, suggesting changes in polymer-neutralizer interaction. Anhydrous gels exhibit 2 different carbonyl stretch bands: the one at ~1653 cm^{-1} is related to the carboxyl group that is hydrogen bonded and is akin to hydrous gels; the second one at ~1717 cm^{-1} is indicative of free carbonyl groups. The carbonyl bands of dried gels appear at different energy levels than the solvated gels. This shift resulting from solvent evaporation, reported for the first time, indicates changes in hydrogen bond characteristics. The results show that FTIR can be a good technique compared with other more time-consuming means of analysis for topical formulations.

INTRODUCTION

Topical gel formulations are used extensively in pharmaceutical and personal care products (lotions, shampoos, etc).[1-3]

Corresponding Author: Chrisita Ackermann, Pharmacokinetics, Dynamics and Metabolism, Preclinical Development and Biotransformation, Pfizer Inc, Ann Arbor, MI 48105. Tel: (734) 622-1348. Email: Chrisita.Ackermann@pfizer.com.

Cross-linked polymers act as thickeners in many topical gels.[4,5] Carbopol 980 NF was used as the thickener in this study because of its wide use in commercial topical gel formulations.[6] Addition of a small amount of surfactant or neutralizer can alter the polymer conformation and the viscosity of the dispersion. Neutralizer works primarily by forming ion-pairs.[7] The surfactants, on the other hand, act through hydrophobic interaction between the nonpolar surfactant tail and the polymer backbone or solvent, and through electrostatic interactions between the polar heads of the surfactant and the charged group of the polymers.[7] Depending on the choice of the polymer and solvent, one or both mechanisms is responsible for gel formation. When the polymers uncoil because of the formation of hydrogen bonds or electrostatic interaction, the gel structure is formed. The networked gels are very useful as platforms in drug delivery applications since controlled release of medicaments is possible.[8,9] Different solvent systems are used to satisfy compatibility requirements with active drugs and/or other excipients, and to ensure bioavailability of the drug when applied on skin.

Polymer-solvent-neutralizer and polymer-solvent-surfactant interactions modify the viscosity, elasticity, and other important properties, and contribute to the stability of the gels.[10] These interactions can significantly affect the medicament diffusion from the gel to skin for transdermal delivery of drugs.[7] This is especially important in case of topical gels because the interaction may change during solvent evaporation when the gel is applied on skin. Also the bioavailability of drugs changes owing to solvent evaporation.

Vibrational spectroscopic techniques are becoming increasingly important and popular in pharmaceutical industries because they are nondestructive in nature, can be applied on-line, and have the potential of providing rapid and convenient solutions to routine analytical problems.[11,12] Information about molecular structure of complex mixtures can be obtained from Fourier transform infrared (FTIR) spectroscopic analysis.[13,14] The ease of sample preparation and operation, and nondestructive nature of analyses make FTIR attractive as a characterization technique to analyze gel formulations. Most organic molecules are IR sensitive.[15] Hence strong spectral response can be obtained for qualitative and even for quantitative analysis. The advent and ease of use of the attenuated total reflectance (ATR) accessory have made it

Table 1. Compositions and pH of Aqueous Carbopol Gel Formulations*

Sample	Water % (wt/wt)	Glycerin % (wt/wt)	Propylene Glycol % (wt/wt)	TEA % (wt/wt)	Carbopol 980 NF % (wt/wt)	pH
AQ1	68.5	1.0	30.0		0.5	3.1
AQ2†	68.5	1.0	30.0		0.5	5.8
AQ3	68.87	1.0	30.0	0.13	0.5	5.1
AQ4	67.6	1.0	30.0	0.9	0.5	8.0

*TEA indicates triethanolamine; and AQ, aqueous formulation.
†0.1N NaOH was added to increase pH from 3.1 to 5.8.

possible to analyze semisolid dosage forms without following extensive sample preparation procedures.

The primary objective of this study was to understand Carbopol-neutralizer and Carbopol-surfactant interactions in different cosolvent systems: aqueous, anhydrous, and hydroalcoholic. To the best of our knowledge, such direct and comprehensive comparisons for various solvent systems are not reported in the literature.

The cosolvent systems were chosen to closely resemble the compositions typically used in commercial topical gel formulations. This is of utmost importance from practical point of view because solvents such as glycerin and propylene glycol can alter drug delivery characteristics of topical gels owing to the changes in polymer-surfactant/polymer-neutralizer interactions. Most of the current literature on spectroscopic measurements of polymer dispersions involves only a single solvent instead of a cosolvent system as used in the present study.

The second objective was to investigate the potential of FTIR for determining the end point during addition of surfactant or neutralizer (ie, amount of surfactant or neutralizer required to obtain optimum gel quality). In an aqueous system, the end point can be evaluated by monitoring the pH. However, in anhydrous systems there is no equivalent criterion.

The third objective was to identify changes between polymer-surfactant or polymer-neutralizer interactions during solvent evaporation. This is of great consequence since solvent evaporation is inevitable during and after application of topical gels on skin.

MATERIALS AND METHODS

Materials

Carbopol 980 was obtained from Noveon (Cleveland, OH). Distilled deionized water was used to prepare gels. The triethanolamine (TEA) 98% solution was obtained from Sigma-Aldrich (St Louis, MO). Anhydrous glycerol (99.9% purity) was purchased from JT Baker (Phillipsburg, NJ), ethyl alcohol (*United States Pharmacopeia* absolute 200 proof grade) was obtained from Aaper Alcohol and Chemical Co (Shelbyville, KY), whereas propylene glycol was pur-

chased from Sigma. Ethomeen (grade C/25, trademark of Akzo-Nobel) was purchased from Garo Enterprises (Chicago, IL).

Gel Formulation

Aqueous Gel. Appropriate quantities of Carbopol 980 NF were added to deionized water and mixed using Omni Mixer Homogenizer (model M50, Omni International Inc, Warrenton, VA). These mixtures were stirred for 30 minutes. Then, preweighed amounts of propylene glycol and glycerol were added to the mixture, and the mixture was stirred for an additional 20 minutes. The dispersion was allowed to hydrate and swell for 60 minutes. The pH of the unneutralized sample (AQ1) was then measured. In case of neutralized samples, 98% TEA (or 0.1N NaOH) was added to Carbopol dispersions until the desired pH value was approximately reached (5.0, 6.0, 8.0). During neutralization, the mixtures were stirred gently with a spatula until homogeneous gels were formed. The pH values were measured in situ and after 5 days with a digital Accumet 25 pH meter (Fisher Scientific International Inc, Hampton, NH). All the samples were allowed to equilibrate for at least 5 days at room temperature prior to performing FTIR measurements. The concentrations (weight fraction) of different components as well as the pH values (after 120 hours) of the products are given in Table 1.

Anhydrous Gel. Carbopol 980 NF was added to ethanol and mixed using Omni Mixer Homogenizer (Model M50) for 30 minutes. Then preweighed amounts of glycerol were added to the mixture and agitated for an additional 20 minutes. The dispersion was allowed to hydrate and swell for 60 minutes. In a separate beaker, appropriate quantities of TEA (98%) or ethomeen were dissolved in propylene glycol. The surfactant/neutralizer solution was subsequently added to the Carbopol dispersion. The mixtures were stirred gently with a spatula until homogeneous gels were formed. All the samples were allowed to equilibrate for at least 5 days at room temperature prior to the evaluation of their FTIR spectra. The compositions of these formulations are shown in Table 2 and the chemical formula of ethomeen is shown in Figure 1.

Hydroalcoholic Gel. A cosolvent was prepared: a mixture of water, ethanol, and propylene glycol. Carbopol 980 NF was

**Table 2.** Compositions of Anhydrous Carbopol Gel Formulations*

Sample	Ethanol % (wt/wt)	Glycerin % (wt/wt)	Propylene Glycol % (wt/wt)	TEA % (wt/wt)	Ethomeen % (wt/wt)	Carbopol % (wt/wt)
AH1	60.0	10.0	27.0		2.0	1.0
AH2	59.5	10.0	27.0		2.5	1.0
AH3	59.5	10.0	28.0	0.5		2.0
AH4	59.0	10.0	28.0	1.0		2.0
AH5	60.0	10.0	28.0			2.0

*TEA indicates triethanolamine; and AH, anhydrous formulation.

Table 3. Compositions and pH of Hydroalcoholic Gel Formulations*

| Sample	Water % (wt/wt)	Ethanol % (wt/wt)	Propylene Glycol % (wt/wt)	TEA % (wt/wt)	Carbopol % (wt/wt)	pH
HA1	27.5	70.0	1.0	0.5	1.0	4.9
HA2	27.5	69.75	1.0	0.75	1.0	5.7

*TEA indicates triethanolamine; and HA, hydroalcoholic formulation.
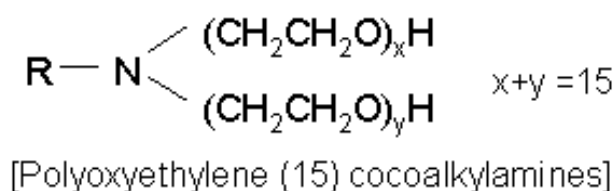
Figure 1. Chemical structure of surfactant ethomeen.

added to the cosolvent and mixed using Omni Mixer Homogenizer (model M50) for ~30 minutes at room temperature (22°C) to form a homogeneous dispersion. The dispersion was then allowed to hydrate and swell. A preweighed amount of TEA (98%) was added to water in a separate container to form a homogeneous solution. The TEA solution was subsequently added to the Carbopol dispersion. The mixtures were stirred gently with a spatula until homogeneous gels were formed. All the samples were allowed to equilibrate for at least 5 days at room temperature prior to the evaluation of their FTIR spectra. The compositions of these formulations are shown in Table 3.
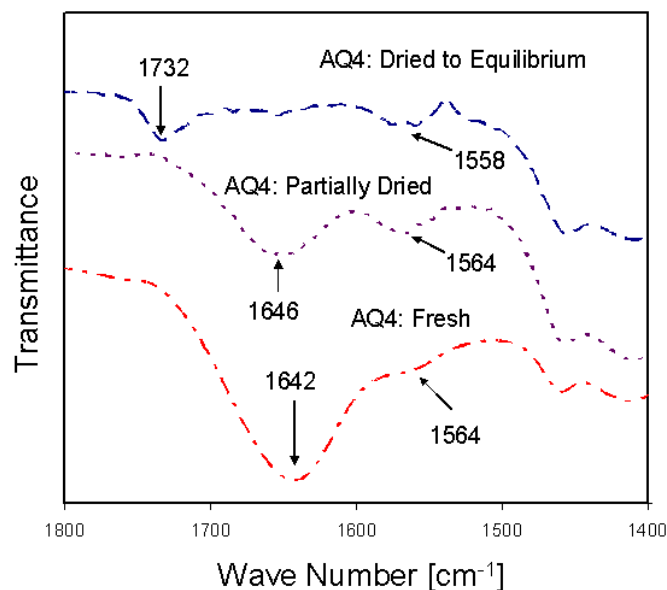
Fourier Transform Infrared Spectroscopic Measurements

The IR spectra of topical gel formulations were collected with a Perkin-Elmer Spectrum BX FTIR spectrometer (Wellesley, MA). The Spectrum BX is a bench-top FTIR capable of routine mid-IR work (4000 cm^{-1} to 400 cm^{-1}). The spectrometer was equipped with an attenuated total reflection (ATR) accessory with a ZnSe crystal. A thin film of each sample was spread directly on the ZnSe crystal for measurement. No other sample preparation was required. The ATR accessory is specifically suited for aqueous gel formulations because the massive –OH water band is attenuated by ATR, and sample bands at longer wavelengths become enhanced. The resolution was 4 cm^{-1} and 15 co-averaged scans were used. It was determined previously that ~10 co-averaged scans produce spectra of desired quality, and increasing the number did not improve the quality of the spectra.
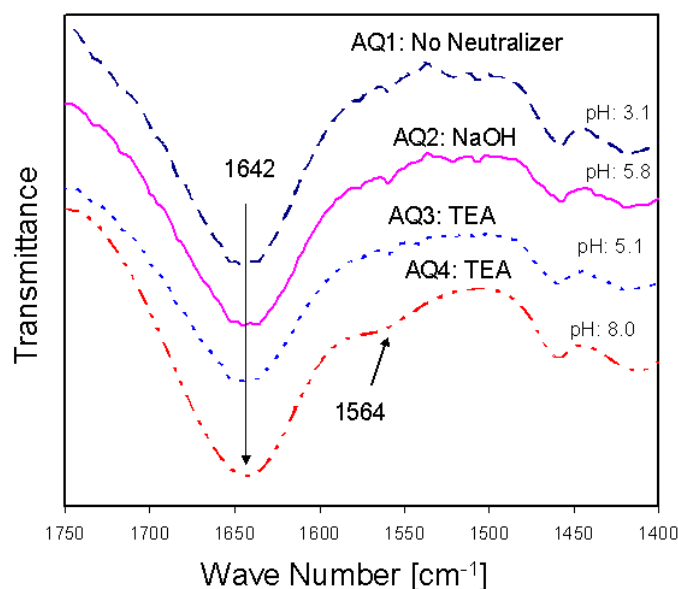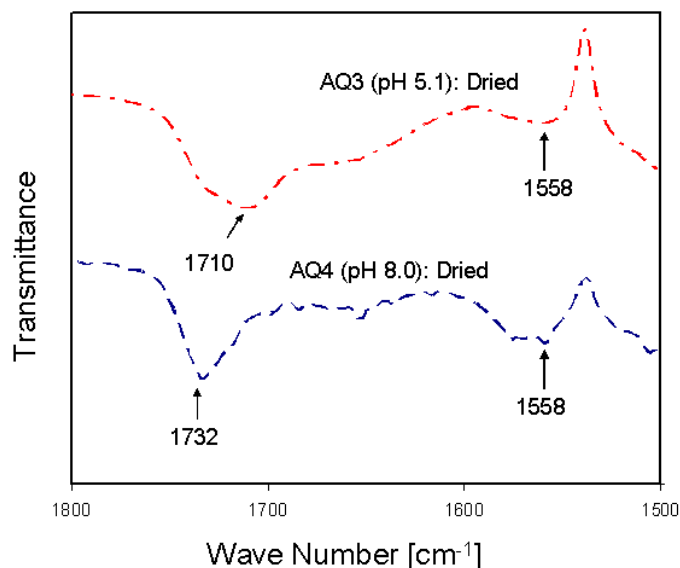

Figure 2. Infrared spectra of various aqueous gels neutralized to different pH.

RESULTS AND DISCUSSION

Figure 2 shows the FTIR spectra of aqueous gel samples neutralized to different pH values. No neutralizer was used for sample AQ1. All the other samples except AQ2 were neutralized with TEA. AQ2 was neutralized with NaOH. The strong band at 1642 cm^{-1} is due to the carbonyl stretch of the carboxylic group of the Carbopol polymer. The structure of Carbopol after neutralization in aqueous media is described by Kemper et al.[15] Upon neutralization, gel formation is thought to occur through hydrogen bonding and through ionization of the carboxyl group.[6] However, the contribution of individual bond types in forming the gel is not known. The carbonyl band observed at 1642 cm^{-1} is at a lower energy level compared with the carbonyl stretch at 1700 cm^{-1} reported by Barreiro-Iglesias et al.[7] However, the authors measured the spectrum in dry state. The shift from ~1700 cm^{-1} to
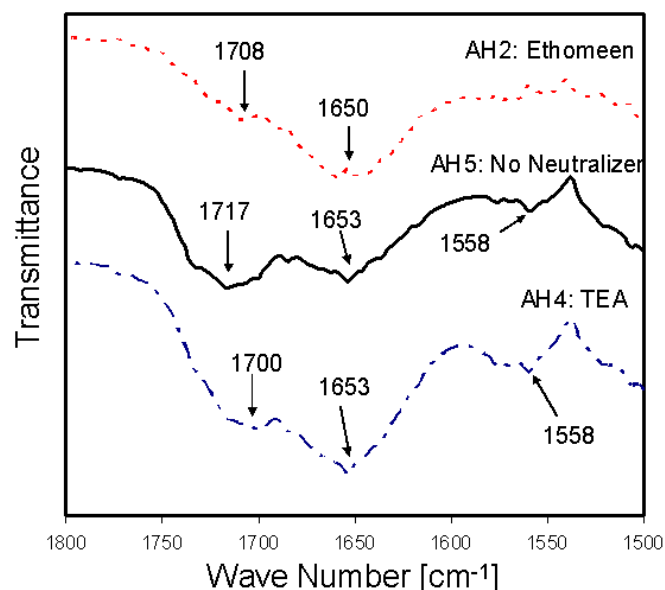
Figure 3. Change in FTIR spectra of an aqueous Carbopol gel due to water evaporation.


Figure 5. Comparison of spectroscopic measurements of anhydrous gels formulated with different neutralizers.

so prominent. The presence of polar solvents such as glycerin and propylene glycol seems to be responsible for the increased hydrogen bonding between solvent and polymer.
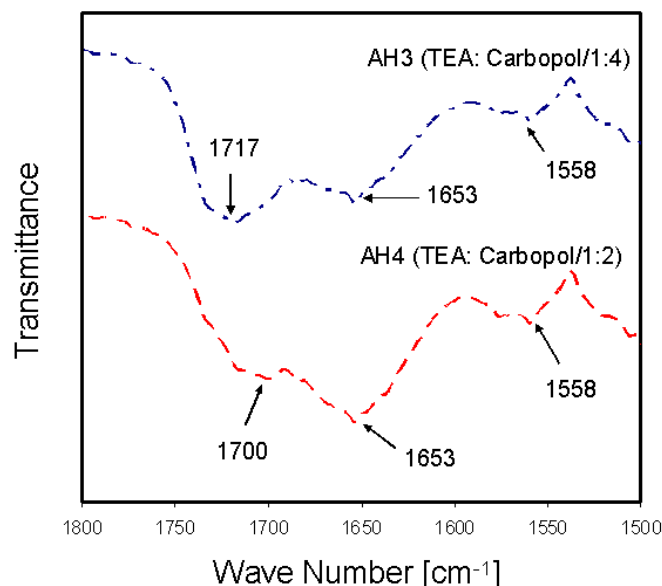
Figure 3 shows the IR spectra of sample AQ4 (pH 8.0) after different states of drying. The initial mass of a predetermined amount of AQ4 was measured, and the masses of the same sample were measured after different states of drying. Since vapor pressures of glycerin and propylene glycol are very low compared with the vapor pressure of water, it can be assumed that the mass losses are only due to the evaporation of solvent water. In partially dried AQ4, 91.2% of the water present initially had evaporated; the equilibrium dried curve represents the gel sample after it had been dried for at least 30 days at room temperature (22°C). The evaporation of solvent water causes the shift of the carbonyl stretch to higher energy (1732 cm^{-1}). This band is similar to the peak observed by Barreiro-Iglesias et al at 1730 cm^{-1} for dried Carbopol polymers gellified with Pluronic F-127.[10] The authors also reported that the CO peak of ungellified Carbopol occurred at 1700 cm^{-1}. The shift from 1700 cm^{-1} to 1730 cm^{-1} was an indication of the interaction between the polymer and the Pluronic surfactant. The same trend is observed for sample AQ3 neutralized to a pH of 5.1 (Figure 4). However, the dried state of this sample displays carbonyl peak at 1710 cm^{-1}. In Figure 4, the shift from 1700 cm^{-1} is more for the higher pH sample as opposed to the lower pH sample. Also, the relative contribution of the ionized carboxyl band increases as the concentration of TEA (ie, pH of the gel) is increased.

Figure 4. IR spectra of aqueous gel samples at equilibrium water content after 30 days of drying.

1642 cm^{-1} indicates a modification of the hydrogen bond interactions from the dry to the hydrated state.

The second notable finding is the absence of the strong ionized carboxyl peak even at pH 5.1 for TEA (sample AQ3) and pH 5.8 for NaOH (sample AQ2). Even at pH 8.0 the ionized carboxyl peak at 1564 cm^{-1} is much weaker than the carbonyl (CO) stretch peak. This is in sharp contrast to the finding of Barreiro-Iglesias,[7] where the authors observed that the ionized peak at 1534 cm^{-1} dominated over the CO stretching peak for a sample with pH 7.4. This contrast suggests the predominance of the ionized peak when the solvent is only water versus in the present case, when the solvent is a mixture of water, glycerin, and propylene glycol, the ionized peak is not

The IR spectra of anhydrous gels with different neutralizers are plotted in Figure 5. Two different carbonyl stretch bands occur: one at 1700 to 1717 cm^{-1} and the other at 1650 to 1653 cm^{-1}. The band at 1653 cm^{-1} is similar to the carbonyl stretch band for aqueous systems and is an indication of polymer-
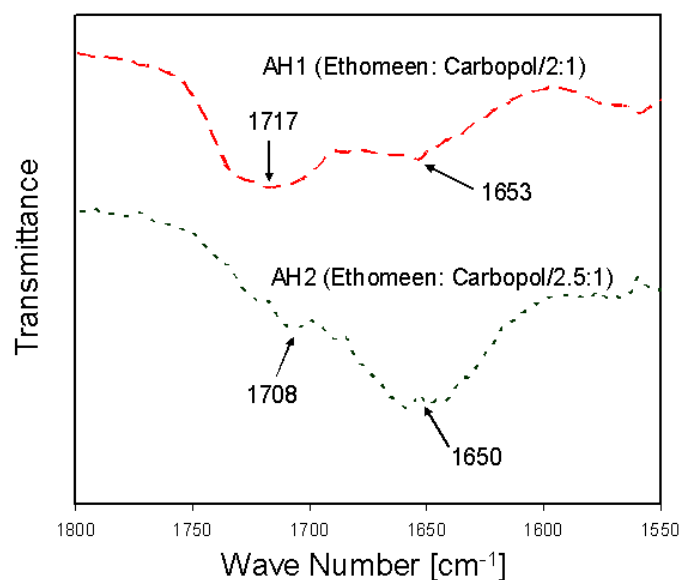
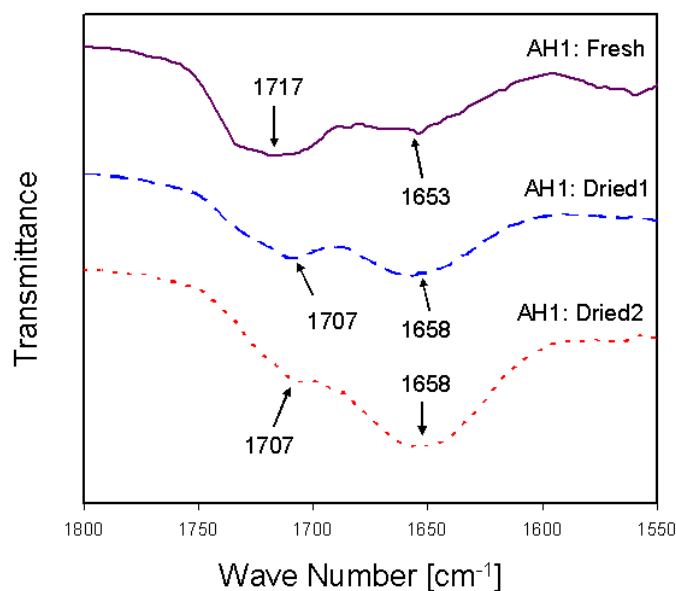**Figure 6.** Comparison of IR spectra of anhydrous gels with different concentrations of ethomeen.

Figure 8. Spectra of anhydrous gels at different states of drying.

Figure 7. Comparison of IR spectra of anhydrous gels with different TEA to Carbopol ratios.

solvent (inferred from sample AH5 where no neutralizer was used) and polymer-surfactant hydrogen bonding. The first band at ~1710 cm^{-1} is due to the free carbonyl group. When surfactant ethomeen (sample AH2) or neutralizer TEA (sample AH4) was added, the percentage of hydrogen-bonded carboxyl group increased and the band at 1653 cm^{-1} became more dominant compared with the band at 1710 cm^{-1}. This finding is more evident at a higher concentration of ethomeen (Figure 6). Therefore, FTIR may be used to monitor progress of gel formation (ie, completion of neutralization) in case of anhydrous solvent systems since a simple criterion such as pH could not be used for these gels.

The ionized carboxylic band at 1558 cm^{-1} is not significant except for sample AH4 (Figure 5) in which a polar neutraliz-

er TEA was used for gel formation. This peak was also observed by Barreiro-Iglesias et al in dried aqueous gels at 1534 cm^{-1}.[7] The ionized carboxyl band is due to the formation of amine salt of Carbopol polymer, which is soluble in polar glycerin and propylene glycol.[16] As expected, the contribution of the peak increased as the concentration of TEA in gel formulations increased (Figure 7). The salt formation is more evident in the gels in which polar neutralizer TEA was used (samples AH3 and AH4).

Comparison of the spectra of AH1 and AH2 having different ethomeen to Carbopol ratios supports the argument of the formation of a surfactant-Carbopol hydrogen bond (Figure 6). As the ethomeen to Carbopol ratio (ie, ethomeen concentration) increases, the contribution of hydrogen-bonded carboxyl group increases. Hence, for a sample with higher ethomeen to Carbopol ratio (AH2), the free carbonyl peak (~1717 cm^{-1}) diminishes and the hydrogen-bonded carbonyl band proportionately enhances (1650 cm^{-1}) (Figure 6). The ratio of the two peak heights can be used to monitor the end point for the gel formation in the case of carbopol dispersions gellified with non-ionic surfactants in a non-aqueous solvent.

Like aqueous gels, evaporation of solvent from anhydrous gels causes a change in interaction between polymers and surfactants (Figure 8). The initial mass of a fixed amount of AH1 was measured, and the masses of the same sample were measured after different states of drying. Since vapor pressures of glycerin and propylene glycol are very low compared with the vapor pressure of ethanol, for anhydrous samples it can be assumed that the mass losses are only due to the evaporation of solvent ethanol. In AH1:Dried1 and AH1:Dried2, the percentages of initial ethanol that had evaporated are 21.4% and 74.7%, respectively. The concentrations of ethanol after drying were calculated to be 54.1% (AH1:Dried1) and 27.5% (AH1:Dried2). Due to the evaporation of ethanol, concentra-
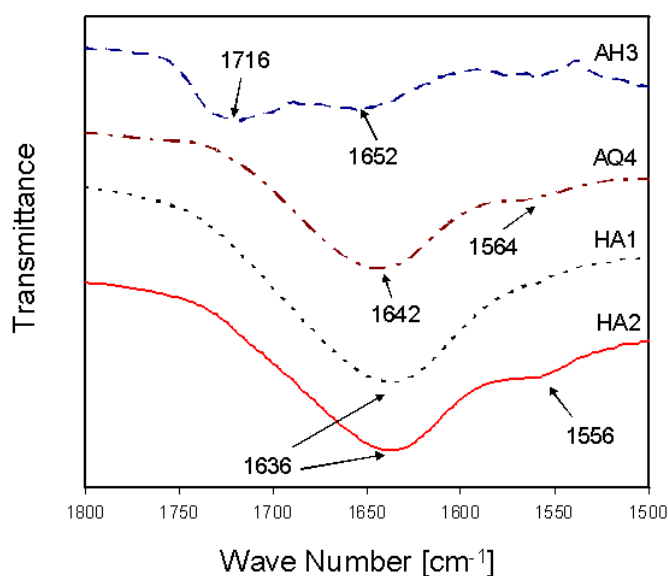
Figure 9. Typical spectral responses of aqueous (AQ), anhydrous (AH), and hydroalcoholic (HA) gels.

tions of polar solvents (propylene glycol, glycerin) in the gel increase. As a result, the amount of free carbonyl groups in the partially dried gels decreases. Therefore, the band corresponding to the hydrogen-bonded carbonyl peak becomes dominant. When ethanol concentration reduces from 60% to 27.5% (AH1:Dried2), the free carbonyl band appears almost indistinguishable compared with the hydrogen-bonded carbonyl band. This change in hydrogen-bond characteristics has the potential to alter the diffusion rate of active drug ingredient in a topical gel formulation. Also drug-polymer or drug-surfactant interactions may change.

We conclude discussion by comparing FTIR spectra of aqueous, anhydrous, and hydroalcoholic gels. Figure 9 displays the spectra of Carbopol gels neutralized with TEA in different solvent systems. In hydroalcoholic gels (samples HA1 and HA2), 70% of the solvent is alcohol and 27.5% is water. Still, it appears that all carboxyl groups of Carbopol are hydrogen bonded and the band at ~1710 cm^{-1} cannot be observed, whereas the band at 1636 cm^{-1} is very distinct (Figure 9). The percentage of ionized carboxylic groups is not significant for HA1, where the pH value of 4.9 is low. However, at a higher proportion of TEA (sample HA2, TEA:Carbopol/0.75:1), the ionized carboxylic group peak is distinguishable (Figure 9). It is noteworthy to mention that for aqueous gels comparable peaks can only be seen at much higher pH (sample AQ4 with pH 8.0).

CONCLUSION

The FTIR-ATR technique was used to understand the hydrogen-bond interaction between Carbopol-neutralizer and Carbopol-surfactant in topical gel formulations. Three different solvent systems were used to formulate gels: aqueous, alcoholic (anhydrous), and hydroalcoholic. The differences in

spectral responses of water- and alcohol-dominated gels suggest polymer-neutralizer interactions are strongly affected by the polarity of the solvent. The spectra of aqueous, anhydrous, and alcoholic gels are also sensitive to the concentrations of surfactant or neutralizer, which can be used to determine optimum surfactant-polymer and neutralizer-polymer ratio. It is also observed that evaporation of volatile solvents from the topical formulations greatly alters the Carbopol-TEA and Carbopol-ethomeen interactions. Results from this study suggest that FTIR can be used as an analytical tool to measure hydrogen bond and electrostatic interactions of Carbopol gel formulations both in the fully hydrated and dried states. The rapid and nondestructive FTIR technique thus will be useful for quality control analysis of topical gel formulations.

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